REMARKS

Claims 51, 53, 54, 56, 59 and 68-77 are pending. Claims 76 and 77 have been amended. The applicants respectfully submit that no new matter has been added. It is believed that this Amendment is fully responsive to the Office Action dated **April 8, 2004**.

Claims 76 and 77 are objected to under 37 CFR 1.75(c) as being in improper form because a multiple dependent claim should recite the claim numbers in the alternative. (Office action paragraph no. 8)

The objection is overcome by the amendment to claims 76 and 77, correcting the wording to recite the claim numbers in the alternative.

Interview Summary

Applicant's agent, Daniel Geselowitz, conducted a personal interview with Examiner Holleran on July 14, 2004. During the course of the interview, the three rejections under 35 U.S.C. 112, first paragraph, and the general issues involved in the rejections under 35 U.S.C. 103(a) were discussed. No agreement was reached, although the Examiner promised to further discuss with her supervisor the rejection under 35 U.S.C. 112, first paragraph, in paragraph no. 11 of the Office action.

Claims 51, 53, 56, 59 and 68-75 are rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the written description requirement. (Office action paragraph no. 9)

The rejection of claims 51, 53, 56, 59 and 68-75 is respectfully traversed and reconsideration of the rejection is respectfully requested.

This rejection is made in response to the amendment of these claims to recite "wherein the sample is determined to be malignant when the calculated ratio is significantly higher or lower than that of the reference fluid sample of the normal thyroid and is significantly higher or lower than that of the reference fluid sample of the benign thyroid," which was made in the Amendment of January 5, 2004, to clarify the claims.

The Examiner now states:

> "The specification does not provide support for all of the possible combinations of comparisons of ratios with benign and normal ratios".

The Examiner refers to Figures 1-5 in this regard, and states:

> "Thus, the specification teaches the case where the ratio of the lectin-reactivity for a malignant thyroid disease differs from the ratio of benign and from normal, where the benign and normal do not appear to be different from each other (Figures 1 and 2); or the case where the ratio of lectin-reactivity of a benign condition is different from normal and the malignant thyroid disease, where the normal and malignant do not appear to be different from each other (Figure 3). The scope of the claims is not in accordance with these two situations. The claims include **the possibility that malignant thyroid disease ratio is higher than normal ratio, but lower than the benign ratio; or the possibility that the malignant thyroid disease ratio is lower than the normal ratio, but higher than the benign ratio. These two possibilities are not supported by the specification as originally filed.**" (emphasis added)

That is, the Examiner's argument is that these two situations are not supported by the specification.

Applicants respectfully disagree. Although "working examples" can serve as part of the written description, it is **not necessary in general to provide "working examples"** in order to provide written description support for the claimed matter. This is certainly true in the case of the two possibilities listed by the Examiner. Applicant notes that MPEP 2163 (I) states:

> "An applicant shows possession of the claimed invention by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams and formulas that fully set forth the claimed invention. Lockwood v. American Airlines, Inc. 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (Fed.Cir. 1997)."

There is no specific mention here of "working examples" as a requirement for written description.

Applicant has explained in the Amendment dated January 5, 2004, how the wording of the specification supports this general recitation. Specifically, Applicant has indicated support in the specification on page 27, lines 5-8, and page 31, lines 8-12. These lines discuss the ratio of Tg(s) not bound to Con A related [i.e., relative] to the amount of total Tg(s) in papillary carcinoma, compared to benign disease such as benign thyroid adenoma, Grave's disease, follicular adenoma or thyroid adenomatous. The ratio of Tg(s) not bound to Con A relative to the amount of total Tg(s) clearly corresponds to the calculated ratio in the present claims, and the specification is clearly addressing comparison to the benign conditions. Applicant also discussed support in the specification on page 27, lines 9-18; page 31, lines 8-18; page 32, line 22, to page 33, line 1; and page 33, bottom line, to page 34, line 8. These lines discuss the ratio determined for malignant tissue in comparison to benign as well as normal tissue.

Claims 51, 53, 54, 56, 59 and 68-75 are rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the written description requirement. (Office action paragraph no. 10)

The rejection is respectfully traversed and reconsideration of the rejection is respectfully requested.

The Examiner states:

> "The basis for this rejection is that the claimed methods are not described to the extent that the claimed methods read on methods comprising the use of "specific antibodies capable of binding to a specific structure of a sugar chain of a first type of thyroglobulin. ... The specification **fails to provide any examples** of antibodies that are capable of binding to a specific structure of a sugar chain of a first type of thyroglobulin ...." (emphasis added)

As with the previous rejection, it appears that the rejection is based on the lack of **working examples** of antibodies in the specification. Applicant again respectfully argues that this does not constitute proper grounds for rejection, as there is no requirement of working examples in order to satisfy the written description requirement. The specification clearly discloses use of "protein binding to a specific sugar chain structure," including antibodies reactive with Lewis type sugar chains, in the present invention (see, for example, page 6, lines 7-12).

Claims 51, 53, 54, 56, 59 and 68-75 are rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the written description requirement. (Office action paragraph no. 11)

The rejection is respectfully traversed, and reconsideration of the rejection is respectfully requested.

The Examiner states:

> "The basis for this rejection is that specification fails to provide a description of the reference ratios that are required for operation of the claimed methods. ...
>
> However, the specification makes no statements that the exemplified ratios for normal or benign thyroids are exemplary for samples derived from patients, and therefore, the specification fails to describe the reference ratios that are required for operation of the claimed inventions."

That is, the Examiner appears to indicate that because "exemplified ratios", i.e., specific values for the reference ratios, were not recited, written support is lacking.

Applicant respectfully argues that the Examiner's reasoning is improper. The lack of recitation of **specific values** of the reference ratios in the claims does **not** mean that there is a lack of written support for the term "predetermined ratios from a reference fluid sample ..." recited in the claims. Applicants submit that the Examiner is addressing whether there is support for a limitation (i.e., specific numerical values) that is **not in the claims**.

The term "**predetermined** ratios" in the claims clearly indicates that appropriate ratios must be determined using the methods in the claims for the reference fluid samples before the malignancy of the actual "fluid sample originating from a living body" can be determined.

Applicants submits that it is apparent that the specific values of these "predetermined ratios" will depend on the particular lectins or antibodies used, as well as the particular experimental conditions. Specific values given for one set of conditions would not necessarily be useful under other conditions in which the claimed methods were carried out. The term "predetermined ratios" therefore implies an implicit method step of predetermining the ratios for the reference samples, but Applicant submits that this is clear from the wording of the claim and this is fully supported by the

specification. For example, the disclosed comparisons of the "obtained ratio" to that for tissue of Graves' disease or benign thyroid adenoma, requires that the ratio be obtained on these reference samples before the comparison can be made.

Claims 51, 53, 54, 56, 59, 68, 69 and 74 are rejected under 35 U.S.C. §103(a) as being unpatentable over either Nakamura (U.S. Patent No. 5,571,729; issued 11/5/1996) or Satomura (U.S. Patent No. 5,780,247; issued 7/14/1998, effective filing date 11-5-91) in view of either Yamamoto (of record), Tarutani (of record) or Survilo (Survilo, L.I. et al., Vestsi Akademii Navuk Belarusi, Seryya Kimichnykh Navuk, 4:103-107, 1997; abstract only). (Office action paragraph no. 12)

The rejection of claims 51, 53, 54, 56, 59, 68, 69 and 74 is respectfully traversed.

In the present invention, the total amount of thyroglobulin, and an amount of a first type of thyroglobulin having a specific sugar chain structure and/or an amount of a second type of thyroglobulin having a sugar chain structure other than the specific sugar chain (by using an anti-thyroglobulin antibody for measuring thyroglobulin) are measured, followed by determining the malignancy of the thyroid tumor by using a calculated **ratio** based on the total amount of thyroglobulin and the amount of the first type of thyroglobulin and /or the amount of the second type of thyroglobulin.

In the Declaration under 37 CFR 1.132 filed on February 21, 2003, Applicant noted the following points regarding the present claims. The **amount** of thyroglobulin from a malignant thyroid tissue **cannot** distinguish from an amount of thyroglobulin from a normal thyroid tissue, and

cannot distinguish from an amount of thyroglobulin from a benign thyroid tissue. In contrast, the **ratio** of an amount of thyroglobulin from a malignant thyroid tissue, for instance, [an amount of thyroglobulin bound to LCA] / [an amount of total thyroglobulin], **can** distinguish from the ratio from a normal thyroid tissue, and can distinguish from the ratio from a benign thyroid tissue. Therefore the malignancy of thyroid tumor can be determined by comparing **ratios** as recited in the present claims (see Declaration under 37 CFR 1.132 filed on February 21, 2003, Fig. 1 to Fig. 4).

However, Nakamura, Satomura, Yamamoto, Survilo do not teach a method for determining malignancy of thyroid tumor by using a **ratio**. Moreover, Tarutani does not disclose the ratio recited in the present claims, that is, of [Con A-gel unbound Tg or Con A-gel bound Tg] / [the total Tg].

The Examiner asserts that Yamamoto teaches that thyroglobulin isolated from malignant thyroid tumor tissue has a different DEAE-cellulose ion exchange elution pattern from thyroglobulin isolated from benign and from normal thyroids (Office action p.9, lines 19-21). However, Yamamoto is silent on any **ratio**.

Yamamoto does not show the measurement of an amount of thyroglobulin. On p.135, Fig. 1, of Yamamoto, human thyroglobulin was purified, **digested by the action of exhaustive pronase**, subjected to DEAE-cellulose ion exchange chromatography (Yamamoto, p.133, column 2, MATERIALS AND METHODS, *Isolation of oligosaccharid.es from human thyroglobulin,* p.134, column 1, *Fractionation of oligosaccharides).* On p.139, Fig. 5, of Yamamoto, purified thyroglobulin was **digested by the action of exhaustive pronase**, subjected to DEAE-cellulose ion exchange chromatography, eluted with a linear concentration gradient of NaCl, subjected to Con A-Sepharose chromatography and RCA-Sepharose chromatography (p.134, column 1, *Fractionation of*

oligosaccharides). That is, Yamamoto compares the elution pattern of **digested product** of thyroglobulin from a malignant thyroid tissue with that of digested product of thyroglobulin from normal thyroid tissue.

That is, Yamamoto **does not** measure the amount of thyroglobulin, nor compare an amount of thyroglobulin itself from a malignant thyroid tissue with that from a normal thyroid tissue. Applicant therefore disagrees with the Examiner (Office action page 10, lines 12-15) that Yamamoto provides teachings that allow one to predict that lectin affinity may be used as the basis for an assay to differentiate thyroglobulin secreted from a thyroid tumor from thyroglobulin secreted from a non-cancerous thyroid.

The Examiner asserts that Tarutani teaches that the percent of total thyroglobulin that binds to Con-A is different for trabecular carcinoma compared to either follicular adenoma (a benign condition) or normal thyroid tissue (see page 855, Table II) (Office action p. 11, lines 1-3).

Although Tarutani shows the ratio of [Con A-gel unbound Tg or Con A-gel bound Tg] / [the total Tg] from malignant thyroid tissue and from a normal thyroid tissue and that from a benign thyroid tissue (Tarutani, p.855, TABLE II), used amounts as thyroglobulin are derived from water soluble protein but not thyroglobulin itself. Tarutani, p.852, left column under *"Thyroid Glands,"* states:

> "Thyroid tissues were sliced and soluble proteins were extracted in the buffer used for the con A-gel affinity chromatography. The supernatant, obtained after centrifugation, was used to prepare thyroglobulin."

And, under *"Isolation of thyroglobulin on a Concanavalin A-Sepharose column,"* states:

> "A solution of the thyroid extract was applied to the column, and the unadsorbed protein was removed by extensive washing with the buffer. Protein adsorbed on the column was eluted with MeG dissolved in the buffer."

In addition, Tarutani measures an amount of thyroglobulin as the amount of water soluble protein

by absorbance of $E^{1\%,\,1\,cm}_{280nm}$ (Tarutani, p. 852, column 2, lines 1-2).

Therefore, Tarutani does not disclose the measurement of thyroglobulin using anti thyroglobulin antibody and the ratio of [Con A-gel unbound Tg or Con A-gel bound Tg] / [the total Tg] as in the present claims.

As discussed above, Yamamoto does not show the measurement of an amount of thyroglobulin, nor suggest the use of any ratio. Survilo is also silent on the ratio. And Tarutani does not show the measurement of an amount of thyroglobulin using the anti-thyroglobulin antibody and the ratio of [Con A-gel unbound Tg or Con A-gel bound Tg] / [the total Tg] as in the present claims.

Applicants therefore assert that the present claims are not obvious over all the cited references, taken separately or in combination. Reconsideration of the rejection is respectfully requested.

Claims 70 and 71 are rejected under 35 U.S.C. §103(a) as being unpatentable over Katoh (U.S. Patent No. 5,591,589; issued 1-7-97) in view of either Yamamoto (of record), Tarutani (of record) or Survilo (Survilo, L.I. et al., Vestsi Akademii Navuk Belarusi, Seryya Kimichnykh Navuk, 4:103-107, 1997; abstract only). (Office action paragraph no. 13)

The rejection of claims 70 and 71 is respectfully traversed.

Applicants submits that Katoh, Nakamura, Satomura, Yamamoto, Survilo do not teach the method for determining malignancy of thyroid tumor by using the recited **ratio**. In particular, as discussed above, Tarutani does not teach the use of the ratio [Con A-gel unbound Tg or Con A-gel bound Tg] / [the total Tg], as recited in the present claims, for determining malignancy of a thyroid tumor.

Therefore, claims 70 and 71 are not obvious over the cited references, taken separately or in combination.

Claim 73 is rejected under 35 U.S.C. §103(a) as being unpatentable over Canfield (WO/87/00289) in view of Yamamoto (of record). (Office action paragraph no. 14)

The rejection of claim 73 is respectfully traversed.

Claim 73 requires in step (d) calculating a ratio of the amount of the first type of thyroglobulin (or of the second type of thyroglobulin) to the amount of total thyroglobulin.

Applicant has discussed Yamamoto above, arguing that Yamamoto does not teach a method for determining malignancy using a **ratio**. Applicant likewise submits that Canfield does not teach a method for determining malignancy of thyroid tumor by using a **ratio**. Applicant therefore submits that no combination of Canfield and Yamamoto can provide the limitations of claim 73, and claim 73 is not obvious over the cited references, taken separately or in combination.

Claim 75 is rejected under 35 U.S.C. §103(a) as being unpatentable over Katoh (supra) in view of Canfield (WO/87/00289) and further in view of Yamamoto (supra). (Office action paragraph no. 15)

The rejection of claim 75 is respectfully traversed.

Applicant has discussed above that Canfield and Yamamoto do not teach a method for determining malignancy of thyroid tumor by using a **ratio** as in the present claims. Applicant similarly asserts that Katoh does not disclose a method using a **ratio** as in claim 75. Claim 75 is not

obvious over the cited references, taken separately or in combination.

Claims 51, 53, 54, 56, 59, 68, 69 and 74 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1 and 5-9 of U.S. Patent No. 5,780,247 (Satomura) in view of either Yamamoto (of record), Tarutani (of record) or Survilo (Survilo, L.I. et al., Vestsi Akademii Navuk Belarusi, Seryya Kimichnykh Navuk, 4:103-107, 1997; abstract only). (Office action paragraph no. 17)

The obviousness-type double patenting rejection of claims 51, 53, 54, 56, 59, 68 and 74 is respectfully traversed.

In traversing the rejection, Applicant notes the arguments in regard to the rejection in paragraph no. 12 of the Office action, under 35 U.S.C. 103(a) over Nakamura, Satomura, Yamamoto, Tarutani and Survilo. In the present rejection, Yamamoto, Tarutani and Survilo are applied for teachings "that thyroglobulin is a glyscosylated protein and that thyroglobulin derived from malignant thyroids contains a different glycosylation pattern ...."

However, Applicant has argued above (in regard to paragraph no. 12 of the Office action) that Yamamoto, Tarutani and Survilo do **not**, in fact, disclose or suggest the use of the ratio of [Con A-gel unbound Tg or Con A-gel bound Tg] / [the total Tg] of the present claims.

Claims 1 and 5-9 of Satomura '247 are of a general method for separating and measuring analytes, and do not mention thyroglobulin. Applicant submits that the proposed combination of Satomura, Yamamoto, Tarutani and Survilo cannot provide the limitations of the present claims.

Claims 70 and 71 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1 and 3 of U.S. Patent No. 5,591,589 (Katoh et al.) in view of either Yamamoto (of record), Tarutani (of record) or Survilo (Survilo, L.I. et al., Vestsi Akademii Navuk Belarusi, Seryya Kimichnykh Navuk, 4:103-107, 1997; abstract only). (Office action paragraph no. 18)

The rejection of claims 70 and 71 is respectively traversed.

In traversing the rejection, Applicant notes the arguments in regard to the rejection in paragraph no. 13 of the Office action, under 35 U.S.C. 103(a) over Katoh, Yamamoto, Tarutani and Survilo. In the present rejection, Yamamoto, Tarutani and Survilo are again applied for teachings "that thyroglobulin is a glyscosylated protein and that thyroglobulin derived from malignant thyroids contains a different glycosylation pattern ...."

As with the rejection of paragraph no. 17, Applicant again submits that Yamamoto, Tarutani and Survilo do **not**, in fact, disclose or suggest the use of the ratio of [Con A-gel unbound Tg or Con A-gel bound Tg] / [the total Tg] of the present claims, and that claims 70 and 71 are not obvious over the combination of these references with claims 1 and 3 of Katoh et al.

In view of the aforementioned amendments and accompanying remarks, claims, as amended, are in condition for allowance, which action, at an early date, is requested.

If, for any reason, it is felt that this application is not now in condition for allowance, the Examiner is requested to contact Applicant's undersigned agent at the telephone number indicated

below to arrange for an interview to expedite the disposition of this case.

In the event that this paper is not timely filed, Applicant respectfully petitions for an appropriate extension of time. Please charge any fees for such an extension of time and any other fees which may be due with respect to this paper, to Deposit Account No. 01-2340.

Respectfully submitted,

ARMSTRONG, KRATZ, QUINTOS,
HANSON & BROOKS, LLP

Daniel A. Geselowitz, Ph.D.
Agent for Applicants
Reg. No. 42,573

DAG/xl
Atty. Docket No. **990701**
Suite 1000
1725 K Street, N.W.
Washington, D.C. 20006
(202) 659-2930

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PATENT TRADEMARK OFFICE

Enclosure: Petition for Extension of Time

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